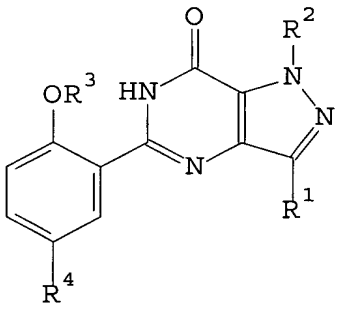
10/088113
JC Rec'd PCT/PTO 15 MAR 2002
PCT/CH00/00409

Medicament for Treatment of Neuropathies

The present invention relates to pharmaceutical agents for treatment of neuropathies, such as, e.g., peripheral diabetic polyneuropathies and gastropareses, as well as general degenerative, toxic, metabolic, ischemic and other autonomous forms of neuropathies in the narrower, namely neurological sense.

Surprisingly, it has been found that compounds of formula (I)



(I)

known, for example, from WO 93/07149 as such and for use as a pharmaceutical agent for cardiovascular disorders, in which

R^1 = C_{1-6}alkyl, optionally substituted by halogen,

R^2 = hydrogen or C_{1-4}alkyl, optionally substituted by halogen,

R^3 = C_{2-4}alkyl, optionally substituted by halogen,

R^4 = $SO_2NR^5R^6$,

C_{1-4}alkyl, optionally substituted with NR^5R^6,

CN, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkenyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

C_{2-4}-alkanoyl, optionally substituted with

NR^5R^6, $SONR^5R^6$, $CONR^5R^6$, CO_2R^7, or halogen,

R^5 and R^6, independent of one another, represent hydrogen or C_{1-4}alkyl, or, together with the nitrogen atom to which they are attached, represent a pyrrolidino, piperidino, morpholino, 4-(NR^8)-1-piperazinyl or 1-imidazolyl ring which, optionally, may be substituted with one or two C_{1-4}alkyl groups,

R^7 = hydrogen or C_{1-4}alkyl, and

R^8 = hydrogen, C_{1-3}alkyl, or hydroxy alkyl with 1 - 4 C atoms, as well as pharmaceutically acceptable salts of such compounds (I), are suitable for chemotherapeutic treatment of neuropathies of the type mentioned above.

In the above definitions, halogen represents fluorine, chlorine, or bromine, fluorine being preferred.

Compounds which correspond or are analogous to this formula, including its salts, and preparation processes of such compounds and salts are known in the art, e.g. from EP 0 463 756, where they have been proposed for prophylactic or therapeutic treatment of cardiovascular diseases. The cardiovascular activity of formula (I) compounds is based on the fact that these compounds are effective and selective inhibitors for cyclic 3',5'-monophosphate phosphodiesterase (cGMP PDE).

It is not known and - respectively - is improbable on the basis of what is known, that this inhibitor effect plays a significant role in neuropathies of the type mentioned. Also, the efficacy of formula (I) compounds for treatment of neuropathies has, in fact, not been determined on the basis of theoretical considerations, but in an empirical manner, and was neither anticipated nor predictable.

Description of Preferred Embodiment

Accordingly, the present invention, in a first embodiment, has for its object a pharmaceutical agent for treatment of neuropathies, characterized in that it consists, at least in part, of at least one compound of formula (I), or at least one pharmaceutically acceptable salt of such a compound, and that it may contain standard auxiliary agents, adjuvants, and carriers, as well as, optionally, additional pharmaceutically active substances.

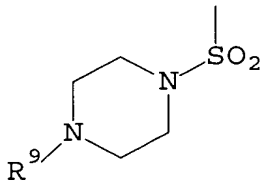
In accordance with a further embodiment, the invention pertains to the use of compounds of formula (I) and/or their pharmaceutically acceptable salts for production of a pharmaceutical agent for therapeutic treatment of neuropathies of the type mentioned above.

In accordance with a third embodiment and to the extent that this is permissible within the framework of national patent laws, the invention is also claimed as a method for therapeutic treatment of neuropathies.

Examples of pharmaceutically acceptable salts of compounds and additional methods of synthesis are also known from the above-noted EP 0 463 756 and, furthermore, from WO 93/07149, as well as from WO 93/06104 and WO 94/05661.

For production of pharmaceutical agents according to the invention, active agents of formula I may be formulated as solid or liquid products with standard adjuvants and carrier substances.

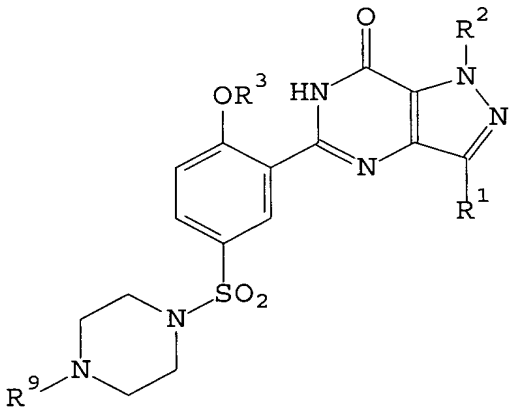
In a preferred group of compounds (I), R^4 represents a group of formula (II):



(II)

particularly if R^1, R^2, R^3, and R^9, respectively, represent alkyl groups with 1 - 4 C atoms, preferably, methyl or ethyl, which, optionally, may be substituted or replaced by halogen, preferably, fluorine.

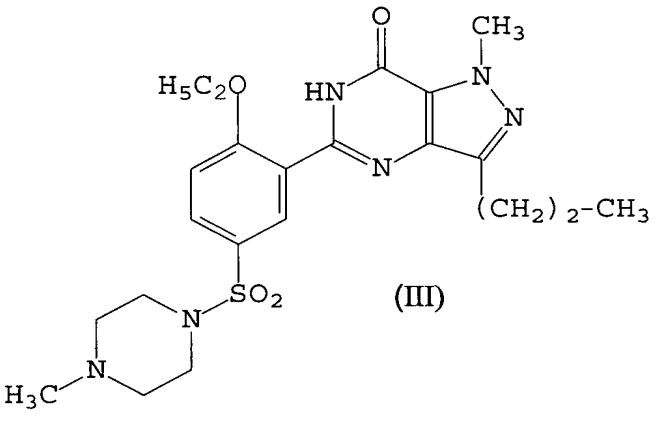
Such compounds correspond to formula (Ia):



(Ia)

in which groups R^1 to R^3 and R^9 have the above-specified meaning.

A preferred specific compound for pharmaceutical agents in accordance with the invention corresponds to formula (III):



(III)

and is the compound known in the art under the generic name sildenafil for treatment of erectile dysfunctions.

Formula (III) compounds and their pharmaceutically acceptable salts can also be prepared in a known manner, e.g., in accordance with the method disclosed in EP 0 463 756.

It is to be expected that effective dosages for treatment of neuropathies will generally be in a similar or lower range as with known medical indications of compounds (1) and (3), respectively, i.e., they will typically be in the range from 1 - 100 mg/day, more specifically, 5 - 50 mg/day, and, typically, 25 - 50 mg/week.

The invention will be explained further by means of examples which are not limiting.

Example 1

A male patient (age 66 years) had been suffering from diabetes mellitus, type 2, for 9 years. While blood glucose values (HbA1c between 6 and 7%) were good, symptoms of a diabetic polyneuropathy appeared, namely vibration sensing of 2/8, no filament sensing, and a reduced hot/cold differentiation. Because of a simultaneous erectile dysfunction he was treated with sildenafil in its commercially available preparation (tablets) at 50 mg/week in a single administration.

Twelve months after start of therapy, a largely normal neurologic situation was reached, namely a vibration sensing of 5/8, intact filament sensing, and hot/cold differentiation. Subjectively, the patient noted disappearance of sensory misperceptions of temperature.

Example 2

A 61-year-old female patient had been suffering from diabetes mellitus, type 1, for about 35 years. Complications included a retinopathy and a painful neuropathy. Under intensified insulin therapy, blood glucose metabolism data were in a sub-optimum range (HbA1c around 8%). Thus, the patient suffered from a painful neuropathy and was treated unsuccessfully with various conventional medicaments.

After medication with sildenafil (50 g/week, each in a single administration of the entire week's dosage), a lasting improvement of symptomatic pain was achieved in the course of the following three months. Objectifiable diagnostic data were improved as well.